REMARKS

1. STATUS OF THE CLAIMS

Claims 1-33 are pending, of which Claims 23-31 were previously withdrawn by the Examiner as being directed to a non-elected invention.[1]

2. REJECTION OF CLAIMS 1-22, 32 AND 33 UNDER 35 U.S.C. §102(b) OVER PAPAYANNOPOULOU *et al.* (WO 94/11027)

The Examiner continued to reject Claims 1-22, and newly rejected Claims 32 and 33 under 35 U.S.C. §102(b) for alleged anticipation by Papayannopoulou *et al.* (WO 94/11027).[2] Applicant respectfully traverses because Papayannopoulou *et al.* fails to expressly and/or inherently disclose the recited step c) of "detecting an altered level of adhesion of said hematopoietic progenitor cells to said target tissue that is not bone marrow endothelial tissue." This is further discussed below.

A. Papayannopoulou *et al.* fails to expressly disclose the recited step c)

Under the law,

> "Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration."[3] The corollary to that holding is that "absence from the reference of any claimed element negates anticipation."[4]

In other words, Papayannopoulou *et al.* anticipates only if it discloses each of the steps of the rejected claims, including step c) of "**detecting an altered level of adhesion of said hematopoietic progenitor cells to said target tissue that is not bone marrow endothelial tissue**." This is not the case because Papayannopoulou *et al.* discloses methods only for altering integrin $\alpha 4\beta 1$'s binding to its ligand in **bone marrow**. This is distinguished from the instantly

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1 Prior Office Action mailed 8/25/2009, page 2, 3rd paragraph.

2 Office Action, page 2, item #4.

3 *W.L. Gore & Assoc., Inc v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303, 313 (Fed. Cir. 1983), cert. denied, 105 S. Ct. 172 (1984), citing *Soundscriber Corp. v. U.S.*, 360 F.2d 954, 960, 148 USPQ 298, 301, adopted, 149 USPQ 640 (Ct. Cl. 1966).

4 *Rowe v. Dror*, 42 USPQ2d 1550, 1553 (Fed. Cir. 1997), citing *Kloster Speedsteel AB v. Crucible, Inc.*, 793 F.2d 1565, 1571, 230 USPQ 81, 84 (Fed. Cir. 1986).

recited "**not bone marrow** endothelial tissue." In particular, Papayannopoulou *et al.*'s methods relate to administering a blocking agent of integrin $\alpha 4\beta 1$ to hematopoietic stem cells in bone marrow, thereby effecting their release (i.e., peripheralization) from bone marrow into peripheral blood. In this regard, Papayannopoulou *et al.* explains that

> "Applicant believes that administering a blocking agent of VLA-4 antigens on the surface of hematopoietic stem cells and CD34+ cells causes peripheralization of these cells by mediating release of the cells from the **marrow** environment via disruption of interactions between VLA-4 and its microenvironmental ligands, such as fibronectin and/or VCAM-1 on stromal cells or in the ECM."[5]

Thus, Papayannopoulou *et al.*'s methods relate to a different tissue (*i.e.*, **bone marrow**) from the instantly recited tissue that is "**not bone marrow** endothelial tissue." Thus, Papayannopoulou *et al.* is conspicuously silent on the recited step c). This precludes express anticipation.

Indeed, in recognition of the reference's failure to expressly anticipate, the Examiner alleged anticipation under only the doctrine of inherency, as further discussed below.

B. **The Examiner has failed to establish Inherency of the recited step c)**

The Examiner alleged anticipation under the doctrine of inherency by arguing that Papayannopoulou *et al.* "does not limit [*sic.*] its method only to bone marrow endothelial tissue" because its methods "would **inherently** result in treating various target tissue that expressed integrin $\alpha 4\beta 1$."[6] This argument suffers from at least two deficiencies.

First, the Examiner's argument does not apply the doctrine of inherency to the claims' limitations. The Federal Circuit explained that

> "Inherent anticipation requires that the missing descriptive material is 'necessarily present,' not merely probably or possibly present, in the prior art."[7]

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5 (Emphasis added) Papayannopoulou *et al.*, page 25, lines 1-9.

6 Office Action, page 3, 4th paragraph.

7 *Trintec Indus., Inc. v. Top-U.S.A. Cor.*, 295 F.3d 1292, 1295, 63 USPQ2d 1597, 1599 (Fed. Cir. 2002) (quoting *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999))

In this instance, the "missing descriptive material" is the claims' limitation of the active step of "**detecting**" an altered level of adhesion of hematopoietic progenitor cells to target tissue that is "not bone marrow endothelial tissue." In other words, inherency must be analyzed in the context of the reference's alleged disclosure of **this particular step**, and not in the context of the reference's allegedly inherent disclosure of a **different step** (as argued by the Examiner) of "**treating** various target tissue that expressed integrin $\alpha 4\beta 1$." Because the Examiner's analysis of inherency did not relate to the claim's limitation as recited in step c), his analysis was improper.

Second, the Examiner's argument falls short of providing the requisite evidence of inherency. The Examiner is respectfully reminded that

> "In relying upon the theory of inherency, the Examiner must provide a **basis in fact and/or technical reasoning** to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art."[8]

> "To establish inherency, the extrinsic **evidence** 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill.'"[9] "Inherency, however, **may not be established by probabilities or possibilities**. The mere fact that a certain thing **may** result from a given set of circumstances is **not sufficient**."[10]

The Examiner did not provide any evidence to demonstrate that Papayannopoulou *et al.* "**necessarily**" carried out the instantly recited step of "detecting an altered level of adhesion of said hematopoietic progenitor cells to said target tissue that is not bone marrow endothelial tissue." In the absence of such evidence, inherency cannot be established.

In summary, Papayannopoulou *et al.* cannot anticipate because it fails to disclose, both expressly and inherently, a limitation of the claims. Accordingly, Applicant respectfully requests

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[8] (Emphasis added) MPEP 2112, citing *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Int. 1990).

[9] (Emphasis added) *In re Robertson*, 49 USPQ2d 1949, 1950 (Fed. Cir. 1999), citing *Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1268, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991).

[10] (Emphasis added) *In re Robertson*, 49 USPQ2d 1949, 1950 (Fed. Cir. 1999), *citing Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1269, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991) (quoting *In re Oelrich*, 666 F.2d 578, 581, 212 USPPQ 323, 326 (CCPA 1981); see also, *Glaxo Inc. v. Novopharm Ltd.*, 52 F.3d 1043, 1047, 34 USPQ2d 1565, 1567 (Fed. Cir. 1995), rehearing denied, in banc suggestion declined (Jun 21, 1995).

that the Examiner withdraw the rejection of Claims 1-22, 32 and 33 under 35 U.S.C. §102(b) over Papayannopoulou *et al.*

3. REJECTION OF CLAIMS 1-22, 32 AND 33 UNDER 35 U.S.C. §112, FIRST PARAGRAPH (NEW MATTER)

The Examiner rejected Claims 1-22, 32 and 33 under 35 U.S.C. §112, first paragraph, on the basis that the step of "detecting altered level of HPC adhesion" allegedly constitutes new matter.[11] Applicant disagrees because the Examiner not only ignored the Specification's teachings, but also mischaracterized Applicant's prior statements, as further discussed below.

A) The Specification teaches that hematopoietic progenitor cells (HPCs) are exemplified by endothelial progenitor cells (EPCs), which are in turn exemplified by endothelial stem cells (ESCs)

In the prior response to the March 11, 2010 final Office Action, Applicant amended Claim 1 to recite "detecting an altered level of **hematopoietic progenitor cell** adhesion to target tissue," and cited as support various teachings in the Specification that related to adhesion of **endothelial progenitor cells** (EPCs) (which are an exemplary hematopoietic progenitor cell) to endothelial cells (which are exemplary target tissue that is not bone marrow endothelial tissue).[12] For example, Applicant referred to the Specification's following teaching:

> "To determine whether **EPCs** can attach to proliferating vascular endothelium that has been stimulated by angiogenic growth factors, we plated **EPCs** labeled with DiI-acetylated LDL onto proliferating endothelial monolayers. **EPCs** bound strongly to endothelium in a $\alpha 4\beta 1$ dependent manner (Figure 17C) and . . . rsVCAM blocked **EPC** attachment to endothelial monolayers (Figure 17D). Similar results were obtained when $\alpha 4\beta 1$ antibodies or rsVCAM were pre-incubated with **EPCs**, but not when they were pre-incubated with endothelial monolayers."[13]

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11 Office Action, page 4, item #6.
12 Specification, Examples 10, beginning on page 86.
13 (Emphasis added) Specification, page 86, 2nd paragraph.

The Examiner now argues that the above disclosure is insufficient because it refers to "the use of $\alpha 4\beta 1$ antibodies to alter adhesion of **EPC** to vascular endothelial, not **HPC**."[14] In other words, the Examiner is taking the position that the Specification's teachings with regards to EPCs do not support teachings regarding HPC. This position is expressly contradicted by the Specification, which says:

> "The term "**hematopoietic progenitor cell**" expressly includes hematopoietic stem cells, **endothelial progenitor cells,** lymphendothelial progenitor cells, mesenchymal precursor cells, myeloid progenitor cells, lymphoid progenitor cells, granulocyte progenitor cell, macrophage progenitor cells, megakaryocyte progenitor cells, erythroid progenitor cells, Pro-B cells and Pro T cells (Terskikh (2003) Blood 102, 94-101)."[15]

In view of the above Specification's teaching that HPCs are exemplified by EPCs, the Specification's teachings with respect to EPCs provide the requisite written description support for the claims' recitation of step of "detecting altered level of HPC adhesion."

Moreover, Applicant draws the Examiner's attention to the Specification's further support of the claims' recitation of step of "detecting altered level of HPC adhesion," which was previously advanced by Applicant in their prior response to the March 11, 2010 final Office Action. In particular, Applicant referred the Examiner to the following exemplary teaching that rs VCAM and anti-integrin $\alpha 4\beta 1$ antibodies (which are exemplary agents that alter specific binding of integrin $\alpha 4\beta 1$ to an integrin $\alpha 4\beta 1$ ligand) blocked adhesion of **endothelial stem cells** (which are exemplary hematopoietic progenitor cells) to endothelial cells (which are exemplary target tissue that is not bone marrow endothelial tissue):

> "To determine whether **stem cells** can attach to endothelial cells (ECs) in an $\alpha 4\beta 1$ dependent manner, we plated fluorescently labeled **stem cells** on confluent EC monolayers, which express the $\alpha 4\beta 1$ ligand VCAM (Figure 34c). **Stem cells** bound strongly to ECs (Figure 34d-e). This **adhesion** was blocked by antibody antagonists of $\alpha 4\beta 1$ but not by control antibodies (anti-$\alpha v\beta 5$) (Figure 34d-e). Attachment was also

[14] Office Action, page 4, 3rd paragraph.
[15] (Emphasis added) Specification, page 18, lines 2-8.

> blocked by recombinant soluble VCAM, a competitive inhibitor of integrin $\alpha 4\beta 1$ function."[16]

Applicant notes that the above-discussed "stem cells" referred to in Figure 34 are "endothelial stem cells" that express CD34+, and are one example of the instantly recited "hematopoietic progenitor cells." This is supported by the following teachings in the Specification.

> "In another embodiment, the **HPCs** comprise CD34+ non-endothelial cells and/or **CD34+CD133+ cells which can differentiate into endothelium (Figure 34a).**"[17]

Furthermore, the Specification expressly says that endothelial stem cells (ESCs) are an example of endothelial progenitor cells (EPCs) by stating

> "Integrin $\alpha 4\beta 1$ Mediates Trafficking of **Endothelial Progenitor Cells**, As Exemplified By **Endothelial Stem Cells**, During Neovascularization."[18]

Because the Specification teaches that HPCs are exemplified by EPCs, which in turn are exemplified by ESCs, Applicant avers that the Specification's teachings with respect to ESCs provide further written description support for the claims' recitation of step of "detecting altered level of HPC adhesion."

In view of the above, the claims' recitation of the step of "detecting altered level of HPC adhesion" enjoys more than adequate support. Accordingly, Applicant respectfully requests withdrawal of the rejection of Claims 1-22, 32 and 33 under 35 U.S.C. §112, first paragraph.

B) <u>The Examiner mischaracterizes Applicant's prior statements</u>

The Examiner noted that endothelial progenitor cells (EPCs) are not exemplary hematopoietic progenitor cells (HPCs) because "the Examiner withdraw prior rejection under 35 U.S.C. 102(e) over WO'03/019136 because of Applicant's statement that WO'03/019136 referring to **EPC that are not HPC**. (See Applicant's comment, mailed on 11/16/09)."[19] This

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16 Example 20 (Specification, page 94, 1st paragraph).
17 (Emphasis added) Specification, sentence bridging pages 2-3.
18 (Emphasis added) Specification, page 47, lines 11-12.
19 (Emphasis added) Office Action, page 4, 3rd paragraph.

mischaracterizes Applicant's prior statements by erroneously implying that Applicant previously stated that HPCs are not exemplified by EPCs. This is not the case.

More particularly, in the prior response mailed on 11/16/09, Applicant disagreed with the rejection of Claims 1-21 under 35 U.S.C. §102(e) for alleged anticipation by Varner (WO 03/019136), and advanced three arguments, none of which supports the Examiner's contention that Applicant stated that "EPC that are not HPC."

Specifically, in the first argument, Applicant previously stated

> "A. Bone Marrow is a Target Tissue in WO 03/019136
> Unlike the instant claims that exclude 'bone marrow endothelial tissue,' the methods of '136 include administering, to **bone endothelial tissue**, agents that inhibit binding of integrin $\alpha 4\beta 1$ to its ligand. These agents are administered in the methods of '136 for the purpose of reducing angiogenesis in bone,[20] such as angiogenesis that is associated with bone cancer.[21] Thus, '136 does not disclose the limitation of target tissue that is 'not bone marrow endothelial tissue.'"[22]

Nothing in the above supports the Examiner's misunderstanding that Applicant stated that "EPC that are not HPC."

In the second argument, Applicant previously stated that:

> "B. WO 03/019136 does not disclose altering adhesion of hematopoietic progenitor cells
> The methods of '136 relate to altering participation of hematopoietic progenitor cells in different phenomena from the recited phenomenon of adhesion. In particular, the methods of '136 employ agents that inhibit binding of integrin $\alpha 4\beta 1$ to its ligand in order to reduce migration of progenitor endothelial cells,[23] and to prevent the participation of

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20 WO 03/019136 says "In particularly preferred embodiments, the invention provides a method for **inhibiting angiogenesis** in a tissue, comprising: a) providing at least one tissue and an agent which inhibits specific binding of integrin $\alpha 4\beta 1$ to an integrin $\alpha 4\beta 1$ ligand; b) treating the tissue with the agent under conditions such that specific binding of integrin $\alpha 4\beta 1$ to the integrin $\alpha 4\beta 1$ ligand is inhibited and a treated tissue is produced; and c) observing inhibition of angiogenesis in the treated tissue . . . In yet another preferred embodiment, the tissue comprises ocular tissue, skin tissue, **bone tissue**, or synovial tissue." (Emphasis added) WO 03/019136, paragraph bridging pages 3-4. See also, page 5, 2nd paragraph.

21 WO 03/019136 says "In an alternative preferred embodiment, the malignant tumor is. . . **bone cancer** . . ." (Emphasis added) WO 03/019136, page 5, 2nd paragraph.

22 (Emphasis in original) Applicant's response mailed on 11/16/2009, page 8.

23 WO 03/019136 says ". . . agents which inhibit the specific binding of integrin $\alpha 4\beta 1$ to one or more of its

endothelial progenitor cells in angiogenesis.[24] The '136's phenomena of **migration and angiogenesis** are distinguished from the phenomenon of "**adhesion**" of hematopoietic progenitor cells that is altered by the instantly claimed methods. Therefore, '136 does not disclose the limitation of altering 'adhesion' of hematopoietic progenitor cells."[25]

None of the above statements by Applicant can logically support the Examiner's allegation that Applicant stated that "EPC that are not HPC."

In the third argument, Applicant previously stated that:

"C. WO 03/019136 discloses altering adhesion of mature endothelial cells, not of hematopoietic progenitor cells

The methods of '136 relate to altering adhesion of a cell type (*i.e.*, of mature **endothelial** cells)[26] that is different from the recited **hematopoietic progenitor** cells. Because '136 lacks this limitation, it does not anticipate the claims."[27]

Nothing in the above supports the Examiner's mischaracterization that Applicant stated that "EPC that are not HPC." In particular, Applicant notes that WO 03/019136 refers to "endothelial cells" (**ECs**), which are **different** from the "endothelial progenitor cells" (**EPCs**) that are one example of the instantly recited hematopoietic progenitor cells (**HPCs**).

Because the Examiner mischaracterized Applicant's prior arguments, there is no inconsistency in Applicant's above discussion (item 3.A.) that the Specification provides ample support for the claims' recitation of the step of "detecting altered level of HPC adhesion."

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ligands block the outgrowth of new blood vessels from pre-existing vessels, and/or block the ability of circulating endothelial cells and/or **progenitor endothelial cells** from leaving the bloodstream and entering and **migrating** through tissues to sites of hypoxia or growth factor secretion where they may participate in the formation of new blood vessels." (Emphasis added) WO 03/019136, page 13, 2nd paragraph. See also Example 12 of '132, entitled "Inhibition of Endothelial Progenitor Cell **Migration** in *In Vivo* Mouse and Rat Animal Models." (Emphasis added) WO 03/019136, page 66.

24 See, Example 18 of '132, entitled "Antagonists of integrin $\alpha4\beta1$ prevent the participation of endothelial progenitor cells in **angiogenesis.**" (Emphasis added) WO 03/019136, page 69.

25 (Emphasis in original) Applicant's response mailed on 11/16/2009, pages 8-9.

26 WO 03/019136 says "Also provided herein are methods for inhibiting **endothelial cell adhesion**, comprising: a) providing endothelial cells and an agent which inhibits specific binding of integrin $\alpha4\beta1$ to an integrin $\alpha4\beta1$ ligand; b) treating the endothelial cells with the agent under conditions such that specific binding of integrin $\alpha4\beta1$ to the integrin $\alpha4\beta1$ ligand is inhibited and treated endothelial cells are produced; and c) observing inhibition of cell adhesion of the treated endothelial cells." (Emphasis added) WO 03/019136, page 4, last full paragraph. WO 03/019136 also discloses that "Figure 3 shows inhibition of **endothelial cell adhesion** (A), and migration (B) by anti-integrin $\alpha4\beta1$ antibody antagonists." (Emphasis added) WO 03/019136, page10, 3rd paragraph. See also WO 03/019136, Example 3, beginning on page 60, entitled "Inhibition of Human Neonatal Cell **Adhesion** to, and Migration of Human Vascular **Endothelial Cells** on, CS-1 Fibronectin by Anti-Integrin $\alpha4\beta1$ Antibody." Emphasis added.

27 (Emphasis in original) Applicant's response mailed on 11/16/2009, page 9.

Accordingly, Applicant respectfully requests withdrawal of the rejection of Claims 1-22, 32 and 33 under 35 U.S.C. §112, first paragraph.

CONCLUSION

Applicant respectfully requests reconsideration of the application in view of the above, which places the claims in condition for allowance. To expedite prosecution, Applicant also respectfully invites the Examiner to **call the undersigned before drafting another written communication**, if any.

The Commissioner is hereby authorized to charge payment of any fees associated with this communication or credit any overpayment to Deposit Account No. **08-1290**.

Respectfully submitted,

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